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Synthetic peptides identified from *Palmaria palmata* enhance glucagon-like peptide-1 stability *in vitro* and show acute anti-hyperglycaemic and insulinotropic actions in mice

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Secretion of the incretin hormone glucagon-like-peptide 1 (GLP-1) from the intestinal L-cells play a significant role in improving glycaemic control following a meal[(1)] but it is rapidly inactivated by dipeptidylpeptidase-4 (DPP-4)[(2)]. Orally active DPP-4 inhibitor drugs are used to improve glycaemic control in people with diabetes. Several peptide component peptides from the edible seaweed *Palmaria palmata* (Dulse) have been identified as having DPP-4 inhibitory actions[(3)]. Here we examined the efficacy of three short synthetic peptides derived from *Palmaria palmata* to stabilise glucagon-like peptide-1(7–36)amide (GLP-1) using an *in vitro* HPLC assay and to affect insulin secretion and glycaemic control in mice challenged with an intraperitoneal glucose tolerance test (ipGTT).

The actions of these peptides, Leu-Leu-Ala-Pro (LLAP), Met-Ala-Gly-Val-Asp-His-Ile (MAGVDHI) and Ile-Leu-Ala-Pro (ILAP) at preserving the stability of the incretin hormone GLP-1 were examined using a HPLC assay. GLP-1 stability was assessed at 0, 2, 8 and 24 h in the presence of porcine DPP-4 (5 mU) at 37°C in triethanolamine buffer (50 mM, pH 7.8) with a fixed concentration (10^{-6} M) of each peptide. In addition, synthetic peptides (10^{-12} to 10^{-6} M) were tested for their ability to promote acute (20 min) insulin secretion from cultured pancreatic BRIN-BD11 cells at 5.6 mM glucose. Finally, peptides were co-administered (25 nmol/kg) by intraperitoneal injection along with glucose (18 mmol, ipGGT) to healthy male NIH Swiss mice and tail blood samples collected at intervals from 0-120 min.

All three peptides LLAP, MAGVDHI and ILAP demonstrated efficacy as DPP-4 inhibitors. GLP-1 control exposed to DPP-4 had a half-life of 1.5 h, but the above synthetic peptides reduced the action of DPP-4 and prolonged the half-life of GLP-1 to 8, 10 and 13 h, respectively, as assessed using an *in vitro* HPLC assay. LLAP and ILAP (but not MAGVDHI) produced a dose-dependent (10^{-11} and 10^{-6} M) increase in insulin secretion (1.4- to 2.0-fold) from cultured BRIN-BD11 cells at 5.6 mM glucose versus controls (Student t-test $P < 0.01$ to $P < 0.001$). When tested *in vivo* in mice LLAP and ILAP produced a 43–52% reduction ($P < 0.05$) in the blood glucose area under the curve ($AUC_{0–120\ min}$) which was accompanied by a 2.9 to 4.4-fold rise in plasma insulin ($AUC_{0–120\ min}$, $P < 0.01$ to $p < 0.001$), compared to the glucose control.

Overall these three synthetic peptides derived from *Palmaria palmata*, helped stabilise GLP-1 against DPP-4 degradation *in vitro*. Furthermore LLAP and ILAP stimulated acute insulin secretion in cultured pancreatic cells, as well as demonstrating potent anti-hyperglycaemic and insulinotropic actions in mice.

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